AMENDMENTS TO THE DRAWING

Please replace Figure 1 with the attached replacement sheet for Figure 1.

REMARKS

Claims 1, 3, 7-8, 10-11, 33-36, and 39-40 were pending in the present application. Claim 40 has been canceled. Claims 1, 3, 7-8, and 10-11 are amended herein. New claims 41 and 42 have been added. No new matter is added thereby.

All pending claims were rejected in the Office Action. In view of the foregoing amendments and arguments that follow, Applicants request withdrawal of all rejections upon reconsideration.

Preliminarily, Applicants note with appreciation that the Office withdrew the rejection over Ledbetter et al. and also withdrew the rejection for obviousness-type double patenting and the rejection under 35 U.S.C. § 112, second paragraph, for omission of essential steps.

The Office notes that multiple references have been cited in the specification that have not been considered because no copies have been provided. An Information Disclosure Statement accompanies this response.

Although it did not do so in this application, the Office objected to the replacement drawing for Figure 1 in Application Serial No. 10/693,308 because it does not label the loxP sites. The replacement drawing for Figure 1 for this application also does not label the loxP sites. Although Applicant believes that the label is unnecessary, Applicant has nevertheless attached to this response an appropriately labeled Replacement Sheet for Figure 1. Applicant emphasizes, however, that the loxP site is not part of his invention. It is simply a convenient means for constructing the loci, but is not the only means. For example, one can also use homologous recombination *in vivo* (see, for example, Rajewsky US 6,570,061 B1) and the replacement of DNA sequences *in vitro* (see, for example, Smithies et al (1985) Nature,317,

230-234).

The Office has objected to claims 7-8 and 10-11 because of informalities in the claim language. Claims 7-8 and 10-11 have been amended herein to correct the informalities. No new matter is added thereby.

Applicants submit that this objection has been overcome.

Priority

The Office determined that the effective filing date of the instant application is the filing date of PCT application PCT/IB02/02303 ("the PCT application"), or April 24, 2002. The Office's position is that, because the claims broadly encompass a loxP site, it must be specifically described in the priority document . The Office further asserts that the priority document fails to provide descriptive support for the loxP site embraced by the breadth of claims 1, 3, 7-8, 10-11, 33-36, 39 and 40. The Office's position is incorrect. Each **potential** method of making encompassed by the claims does not need to be specifically described or enabled.

> The enablement requirement is met if the description enables **any** mode of making and using the claimed invention.

Engel Indus., Inc. v. The Lockformer Co., 946 F.2d 1528, 1533, 20 U.S.P.Q.2d 1300 (Fed. Cir. 1991), emphasis added. The claims do not require loxP sites. Furthermore, as noted above, loxP sites are **not** necessary to the invention. Applicants submit that the correct effective filing date of the instant application is the filing date of the GB priority document, or April 24, 2001.

Rejections Under 35 U.S.C. 112, first paragraph: Written Description

Claims 1, 3, 7-8, 10-11, 33-36, 39 and 40 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claim 40 has

been canceled. Applicant traverses this rejection as applied to the remaining claims.

One of the Office's contentions seems to be that the claims encompass functional homologues, derivatives, or fragments of the various VHH and VH exons or regions, but no homologues, derivatives, or fragments are disclosed. Without conceding the correctness of the rejection, claims 2 and 4 are amended herein to recite that VHH exons comprise VHH coding sequences, and that the VH exons comprise coding sequences that have been mutated to be the same as a Camelid exon, respectively. Support for the foregoing amendments can be found, *inter alia*, on page 9, lines 24-29 and page 10, lines 7-14. No new matter is added thereby.

The Office also asserts on page 7 of the Office Action that the specification additionally fails to disclose the nature of association, presence, or absence of other possible constant region elements. The nature of association of the constant region genes, and the mechanism of combination of variable regions genes with constant region genes, however, is described on page 2, lines 7-20, of the application as filed. Indeed, a textbook containing what is referred to as an "extensive review" is cited therein.

The Office asserts on page 9 of the Office Action that the specification fails to disclose specific elements of the VHH loci that should be deleted, substituted or mutated to produce a functional single heavy chain antibody. Applicant disagrees. As emphasized in the specification, it is the absence of a functional CH1 domain which accounts for the inability of the heavy chain antibodies to associate with light chain. (See page 19, lines 25-28 and page 20, lines 8-12, of the application as filed.) As acknowledged by the Office on page 14 of the Office Action, this was known prior to Applicant's filing date. See Sitia et al., *Cell* 60; 781-90 (1990) (cited in the Supplemental Information Disclosure Statement filed October 19, 2006). Sitia et al

report that light chain binding can be eliminated by deletion of the CH1 region in the IgH gene. *Id.*

Applicant notes that the Office repeatedly states that the specification describes that the *loci* have one or more genes which do not express functional CH1 or CH4. The loci, however, are not so defined – see page 9, lines 17-22; page 10, lines 1-5; and page 18, lines 4-8 and lines 18-23, of the application as filed. Nor is it necessary that CH4 be nonfunctional. A heavy chain only antibody lacking CH1, but not lacking CH4, was secreted by cells and assembled as an antibody complex. See Sitia et al. Thus, while elimination of CH1 functionality is essential to formation of a single heavy chain antibody, CH4 functionality is irrelevant to formation of a heavy chain only antibody. *Id.* Moreover, in man and other mammals, IgG and IgA naturally lack a CH4 domain. CH4 is therefore not functional in the invention .

In the camelid, CH1 functionality is eliminated by an alternative splice. This is discussed as a means of eliminating functionality in the specification. See page 2, line 21 to page 3, line 8 of the application filed. The Office refers to the report in Janssen et al. that a point mutation was not sufficient to allow for expression of the antibody to support its position that the specification does not describe what elements need to be deleted. With all due respect, the Office is missing the point. The invention is sufficiently described, i.e., CH1 must be nonfunctional. Applicant is not required to disclose how to achieve this nonfunctionality to comply with written description. Regardless, on page 11, line 31 through page 12, line 3, the specification discloses that nucleic acid encoding CH1 (and CH4 in this preferred embodiment) can be mutated, **deleted**, or substituted, or otherwise treated so as to be non-functional. Notably, in Sitia et al., CH1 had been deleted.

Applicant requests that this rejection be withdrawn.

Rejection Under 35 U.S.C. 112, first paragraph: Enablement

Claims 1, 3, 7-8, 10-11, 33-36, 39 and 40 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. Claim 40 has been canceled. To the extent this rejection applies to the remaining claims, Applicant traverses.

The Office asserts that the claims broadly embrace using embryonic stem cells ("ES Cells"), nuclear transfer, **and** somatic delivery, but do not adequately enable these procedures. First, the claims have been amended to specifically recite that the mammals are transgenic. A transgenic mammal, by definition, refers to germline transmission of the transgene, not somatic delivery. Support for this amendment can be found, *inter alia*, on page 27, lines 21-23, of the application as filed.

Second, the Office is misapplying the case law regarding enablement. Although claims must be enabled throughout their scope, Applicants only need to disclose **one** method of making and using to satisfy enablement. See *Engel Indus., Inc. , supra.* The Office is inappropriately requiring that every potential method of making and using be enabled in order to meet the scope requirement. This is not the correct interpretation of scope.

> As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of **protection** sought by the claims.

MPEP 2164.08, citing, *inter alia, AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244, 68 USPQ2d 1280, 1287 (Fed. Cir. 2003), emphasis added.

Applicant does not need to disclose and enable every potential method of making and using; Applicant, rather, must enable making and using in all non-human transgenic mammals. Applicant has done so. See the Declaration of Dr. Grosschedl, paragraphs 13-15 and 17.

> Based on the overwhelming evidence available it is not unreasonable to conclude that the invention (methods for the in vivo derivation of heavy chain only antibodies in transgenic non human mammals in response to antigen challenge) using the natural mammalian IgH regulatory elements as set out could equally be applied by those skilled in the art for the derivation of heavy chain antibody (devoid of CH1) as a result of antigen challenge in any non-human mammalian background in addition to the mouse, for example rat, rabbit, pig, goat sheep, cow, monkey, etc. Indeed, the inventor used human regulatory elements in the mouse with success. **Thus, the route described for the derivation of heavy chain only antibody as exemplified in the application and by Janssens et al using the mouse, can be equally applied to any non-human mammalian system.**
>
> Specifically, I note the following.
>
> - The introduction of transgenes into the germline of non-human mammalian systems was well established at the time of filing.
> - Regulatory elements that ensure high levels of B-

> cell specific IgH were well characterised and were known to be present in the human IgH genomic sequence described, moreover these were known to be functional when incorporated in transgenes in non-human mammals at the time of filing.
>
> - At the time of filing, there was a wealth of evidence to demonstrate that enhancer and LCR elements derived from one mammalian species (including human) are functional in other mammalian species.

Declaration of Dr. Grosschedl, paragraph 17, emphasis added. In light of the Office's observation that LCR was not recited in any independent claims, Applicant has amended claims 2 and 4 to recite that the regulatory element comprises an LCR. Support for this recitation can be found, *inter alia*, on page 23, lines 12-14, of the application as filed. Consequently, Applicant has canceled claim 40 and added claims 41 and 42 to be directed to methods in the mouse without requiring an LCR. (Applicant notes that the Office repeatedly incorrectly refers to Dr. Grosschedl as Dr. Drosschedi. Applicant also notes that the second full paragraph on page 26 of the Office Action seems to be misplaced; it discusses use of animals as bioreactors and cites to pages of a reference, but the reference itself is not cited.)

While acknowledging that Dr. Grosschedl's declaration is persuasive to the extent one skilled in the art would be able to express any heterologous transgenic loci comprising any tissue specific regulatory sequence when introducing the transgene into the germline of non-human mammalian systems, the Office maintains its position that the claims are not limited to germline

delivery of the transgene. The claims have been amended to specify that the mammal is a transgenic. As noted above, a transgenic animal has transgenes introduced into its germline.

The Office also states, on pages 22 and 30, that one of skill in the art would have to empirically test whether resulting single heavy chain antibody is complexed with endogenous antibody of wild type nonhuman mammal and an adequate titer is produced to make use of the invention. The undersigned is not sure what the Office means regarding "complexing." As noted above, because the heavy chain only antibodies lack CH1, they cannot complex with light chain, so there is no possibility that the heavy chain having the VHH or camelised VH will complex with a non-camelid or non-camelised light chain.

In support of its argument regarding serum titers, the Office cites the Wagner reference, which reports that low serum titers were obtained until the endogenous locus was disrupted. Wagner et al., *Nucleic Acids Res.* 22(8); 1389-93 (1994). First, a quantifiable titer is not required. At the time of the invention, technology was available for amplification. See the Declaration of Dr. Weiner, paragraphs 20 and 21. See also Ward et al., (1989) *Nature*, 341, 544-546 (cited in the Supplemental Information Disclosure Statement filed October 19, 2006) and EP 0368684B2 **(copy enclosed)**.

Second, the endogenous locus should not interfere with trangene expression because allelic exclusion will ensure that some cells will express only the transgene. One skilled in the art would construct an assembled IgH locus (-CH1) comprising the necessary regulatory elements for B-cell specific expression, and using the technology readily available at the time would generate a transgenic non-human mammal. Analysis of expression of the resulting transgene would show that, while all cells comprise mouse endogenous IgG genes (wt and uMT) and

transgenes, they will express only one locus due to allelic exclusion. See Janssens et al., *Proc. National Academy of Science*, 15130-15130 (2006) and the Declaration of Dr. Grosveld, Figures 2 and 3. Thus, each cell will express either endogenous IgH or a IgH(-CH1) transgene, but not both. Furthermore, expression data in the wt situation shows that the transgene locus is used frequently at the expense of the wt loci. *See* Figure 3F of Janssens et al. Thus, novel heavy chain only antibodies could be readily expressed and amplified using technology routine to those skilled in the art. Heavy chain only antibody could also be readily detected using established technology such as Western blots.

The Office also states that the specification fails to provide the structure of the **specific** transgenic loci in Janssens et al. (See Office Action, pages 23-24.) It is unclear whether the Office's issue is written description or enablement. The statement is cited in a paragraph addressing enablement, so Applicant assumes this is the Office's issue. Notably, no legal precedent is cited in support. Nor is such a showing required. *See* MPEP 2164.05 and MPEP 2164.08, citing *In re Marzocchi*, 439 F.2d 220, 223-224, 169 USPQ 367, 370 (CCPA 1971) (How a teaching is set forth, by specific example or broad terminology, is not important.). The analysis for enablement is not whether the **structure** is provided specifically as set forth in the **post-filing reference** but, rather, whether the claims in the application as filed are enabled. The prior art describes transgenic non-human mammals which co-express functional immunoglobulin heavy and light chain transgenes which respond in a B-cell specific manner to antigen challenge. These teach the assembly of heavy chain loci comprising V, D and J genes, and constant regions which comprise a CH1 region (see, for example, WO/1994/002602 and WO/1993/12227). Moreover Xu and Davis (2000) Immunity, 13, 37-45 **(copy enclosed)** describe a heavy chain

transgene with limited V gene segments and lacking Cu constant regions which also responds to antigen challenge in a B-cell specific manner. Thus, the assembly of complex heavy chain immunoglobulin loci as functional transgenes was well established in the art prior to the filing date. The present invention further teaches and enables that, in the absence of CH1 functionality, heavy chain antibodies lacking light chain are expressed from heavy chain transgenes (now lacking CH1 functionality) in a B-cell specific manner in response to antigen challenge.

Finally, the Office states, on page 19, that, "[a]bsent **evidence** to the contrary, it is not clear that [the regulatory elements] would be functional in other animal species, using any other method of construct delivery in the same manner as they have been demonstrated in the transgenic mouse produced by pronuclear injection of the construct." But, Applicant provided evidence to the contrary. In his declaration, Dr. Grosschedl states that there is no reason to believe that the regulatory elements would **not** work in other animal species and cites WO 02/12437 A2 in support (see the Declaration of Dr. Grosschedl, paragraphs 13-15 and 17). As noted above, Dr. Grosschedl concludes that the method could be applied equally well to any non-human mammalian system (Declaration of Dr. Grosschedl, paragraph 17). The Office has apparently failed to acknowledge Dr. Grosschedl's declaration as evidence. This is error on the Office's part. "A declaration or affidavit is, itself, evidence that must be considered." MPEP 2164.05, emphasis in original.

Applicant requests that this rejection be withdrawn.

CONCLUSION

Applicant respectfully submits that claims 1, 3, 7-8, 10-11, 33-36, and 39-42 are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 665-5593, if there are any questions regarding Applicants' claimed invention.

Respectfully submitted,

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Date: September 29, 2008

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